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PATENT
Docket No. 388512010900

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Dated: January 17, 2007 Signature: Marian Christopher
Marian Christopher

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Patent Application of: Lawrence M. KAUVAR et al.	Confirmation No.: 6212
Application No.: 10/681,013	Examiner: David J. Venci
Filed: October 7, 2003	Group Art Unit: 1641
For: METHODS TO DETERMINE NUMBERS OF PARTICLES IN MULTIPLEXED ASSAYS (AS AMENDED)	

BRIEF ON APPEAL

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

A Notice of Appeal was filed in the present application on 17 October 2006, thus setting a date for filing of the Brief of 17 December 2006. A petition for an extension of time of one (1) month until 17 January 2007 is enclosed along with the required fee. Claims 1-7 are finally rejected and are subject to this Appeal. Reversal of the outstanding rejections and passage of these claims to allowance is respectfully requested.

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1. Real Party in Interest

The Real Party in Interest is the assignee herein, Trellis Biosciences, Inc.

2. Related Appeals and Interferences

Neither appellants, appellants' legal representative or assignee are aware of any patent appeal or interference or judicial proceeding that is related to the present appeal.

3. Status of Claims

The application was filed with six claims which were amended in response to the first Office action and claims 7-9 were added at that time. In response to a final Office action, further amendments were made to claims 1-6 and claims 8-9 were canceled. After filing an RCE, claims 1-3 were again amended and in response to a final Office action claims 1 and 3 were amended and the amendment was indicated to be entered upon Notice of Filing an Appeal.

A Supplementary Amendment was filed but the proposed amendment to claim 1 contained in the Supplementary Response was not entered.

This, claims 1-7 remain pending and are on appeal.

4. Status of Amendments

An amendment in response to final rejection submitted 19 June 2006 was indicated to be entered upon filing a Notice of Appeal, and thus has been entered. A Supplementary proposed Amendment filed 21 August 2006 was not entered.

5. Summary of Claimed Subject Matter

In its most important embodiment, the invention represents an improvement on an old technology that employs "multihued beads." "Multihued beads" have a characteristic hue due to the presence of two or more fluorophores wherein each characteristic hue is a result of varying the ratio of the fluorophores involved. If particles with the same characteristic hue are attached to a reagent designed to bind to a specific target, the nature of a target bound to the label will be evidenced by the characteristic hue.

The improvement provided by the present invention is to add to all particles in a composition containing labels of many different hues, a signal generating moiety, such as a fluorophore, that emits a wavelength different from those participating in the characterizing hues, and which is of the same wavelength, and present in the same amount in all of the multihued beads in the composition. Using the intensity of this standard signal generating moiety as a guide, the number of particles that generate the characterizing hue will be determinable. This is particularly important when the resolution permitting detection of the particles does not permit individual particles to be distinguished. This is explained, for example, on page 2 of the specification in paragraph 6, and instances where this is important are described on page 4 at paragraph 16.

Claim 1 is the sole independent claim. It is directed to a composition comprising a multiplicity of different labels, each directed to a different specific target, wherein each label consists essentially of a particulate support with signal generating moieties and a reagent bound to it. This is described on page 2 of the specification in the first three lines of paragraph 9. Paragraph 9 goes on to describe the other elements of the claim. There is

> at least one moiety which generates a visible signal characteristic of said label and further comprises a second signal generating moiety of standardized intensity... different from that or those which characterize(s) the label ...

The wavelength is thus at the same intensity from all the different labels. It is also a requirement that the wavelength of the signal generated by this standardized moiety (the second signal generating moiety) be different from the wavelengths that compose the characterizing signal. All of this appears on pages 2-3 in paragraph 9. Claim 1 actually does not require "multihued" labels, *i.e.*, the first signal generating moiety can just be a single fluorophore, but claim 2 includes this limitation. Both possibilities are contemplated in paragraph 9 of the specification.

Claim 3 is directed to determining the distribution of target substances in a sample by contacting the sample with the composition of claim 1. The number of the labels at a given location is assessed by measuring the intensity of the second signal generating moiety and the nature of the target is determined by identifying the characterizing signal. All of this is described on page 3 in paragraph 10. The further limitation of claim 4 that the sample is displayed on a support suitable for viewing by microscopy is also supported in that paragraph. Claims 5 and 6 (like claim 4) are as originally filed except for changing "environment" to "sample." The requirement for the diameter range of the particles in claim 7 is found on page 4 in paragraph 16. Intracellular labeling is also supported in this paragraph.

The circumstances that make the improvement of the invention important are illustrated on page 2 in paragraph 6. This is not a feature of the claim, but provides helpful background in understanding why the improvement is useful.

6. Grounds of Rejection to be Reviewed on Appeal

The rejection of claims 1-4 and 7 under 35 U.S.C. § 102(e) as assertedly anticipated by Nie, *et al.* (US 2003/0148544) is evidently maintained as set forth in the Advisory Action. Although this formal rejection has been made throughout prosecution, its rationale has shifted. It is less clear, but appellants assume, that the rejection of claims 5-6 as assertedly obvious over the combination of Nie, *et al.*, in view of Kauvar (US 2001/0044116) is also maintained. In view of the entry of the amendment in response to final rejection, it is believed that the outstanding rejections under 35 U.S.C. § 112, paragraph 2, have been resolved.

7. Argument

Most importantly, with respect to the rejection over Nie for anticipation, appellants request separate consideration of claims 3 and 4 as opposed to claims 1, 2 and 7. Claims 3 and 4 are directed to methods to use the composition of claim 1, wherein there is a specific required step of assessing the number of labels at a location in the sample by measuring the intensity of the signal emitted from the second signal generating moiety attached to the particulate support. This step is clearly not performed by Nie. As will be seen below, the current position of the Examiner, although not explicitly stated, appears to be that the composition claims are inherently anticipated by the coincidental fact that one fluorophore in the characterizing first signal generating moiety is the same in the three types of particles illustrated in Nie's figure 5. It will be clear from the argument below, that there cannot be even accidental anticipation of the method claims, as there is no suggestion that this portion of the characterizing signal be used to assess the number of labels at a location in the sample as required by claim 3 and its dependent claims 4-6.

In addition, with respect to the rejection based on Nie, *et al.,* alone, appellants request separate consideration of claim 2 as compared to claims 1, 3-4 and 7. Although with respect to an anticipation rejection *per se*, the limitations of claim 2 would not further distinguish Nie, in the event that the rejection somehow morphs into an obviousness rejection, the limitations of claim 2 become important because they generate the circumstances in which the improvement of the invention is most useful. If there is only a single moiety generating the characteristic hue, the problem of distinguishing the readout from multiple beads within a detection space does not arise.

It is well established that in order for anticipation to be found, each and every limitation of the claim must be found explicitly or inherently in a single prior art document. Nie does not even inherently disclose the limitation in claim 1 set forth in subparagraph (b) that the particulate support must be coupled to a second signal generating moiety consisting of a single fluorophore directly attached to the particulate support, which second signal generating moiety emits a signal of the same wavelength at the same intensity from all of said different labels and wherein the wavelength generated by the second signal generating moiety is different from the one or more wavelengths that compose the characterizing signal. Nie clearly does not disclose the step, in claim 3 (and therefore 4) of assessing the number of labels at a location in the sample by measuring the intensity of the signal emitted from the second signal generating moiety attached to the particulate support.

In the latest iteration of this rejection (made for the first time in the final rejection mailed 19 April 2006), the Examiner points to paragraph 22 of Nie which describes the embodiments in figure 5. Earlier versions of this rejection, based on paragraph 69 and figure 1 and on paragraph 88 and figure 7 appear to be withdrawn.

As appellants now understand the Examiner's position, it is that a green quantum dot, shown as crosshatched with /, is present at the same level in all four particulate supports shown in figure 5. This position of the Examiner was not at first entirely clear from the formulation of the rejection, either in the final rejection or in the Advisory Action that follows it. However, now that it is apparent that the Examiner regards a portion of what is explicitly set forth in Nie as a characterizing signal as inherently embodying a second signal generating moiety, appellants can acknowledge that the nature of the rejection is at least understood.

However, figure 5 of Nie clearly shows that the green quantum dot is not a "second signal generating moiety" separate from a first characterizing signal generating moiety as required by the claims. The green quantum dot, as shown in the chart at the right-hand side of figure 5, is clearly part of the characterizing signal generating moiety itself. Therefore, it is not a "second signal generating moiety" that emits a signal different from the one or more wavelengths that compose the characterizing signal. It is part of the characterizing signal.

Claims 1, 2 and 7

While the case law regarding accidental anticipation *versus* inherency is by no means easy to apply to any particular set of facts, it does appear that while recognition of the inherent subject matter is not required and that anticipation does not require the actual creation or reduction to practice of the prior art subject matter (*Schering Corp. v. Geneva Pharmaceuticals, Inc.*, 339 F3d 1373, 67 USPQ2d 1664 (Fed. Cir. 2003) rehearing *en banc* denied, 348 F3d 992, 68 USPQ2d 1760 (Fed. Cir. 2003), it is also clear that the assertedly inherent claim limitation must be necessarily and invariably present in the prior art document and not merely probably or possibly present (*Akamai Technologies, Inc. v. Cable & Wireless Internet Svcs., Inc.*, 334 F3d 1186, 68 USPQ2d 1186 (Fed. Cir. 2003)). Appellants believe this requirement is not met.

The Federal Circuit case advancing this last proposition most clearly related in subject matter to the present claims is *Glaxo, Inc. v. Novopharm, Ltd.*, 52 F3d 1043, 34 USPQ2d 1565 (Fed. Cir. 1995) cert. denied 516 U.S. 988 (1995). In this case, a polymorphic form of Zantac® (Form 2) was found to have superior properties for use as a pharmaceutical. A disclosure in an original patent covering an earlier Form 1 contained an example that was asserted to result inherently in Form 2, which was claimed in a later filed patent. It turned out that Form 2 was, indeed, sometimes formed when the procedure of this example was performed, but not always. It was held there could be no assurance that any time the procedure of the example was performed, Form 2 would result, and based on this set of facts, no anticipation was found.

This is in contrast to the situation in *Schering* (*supra*). In *Schering*, a claim was directed to a compound later found to be a metabolite of the drug loratadine that has been disclosed as a pharmaceutical and as administered to humans. Because the metabolite would be formed each and every time loratadine was administered, the production of this compound was assured in every case, and thus anticipated the metabolite claim.

The situation here is similar to that in *Glaxo*. Because the particulate supports described in Nie do not employ, or suggest the employment of, the green quantum dot as a second signal generating moiety, construction of particles according to the instructions set forth in Nie would not necessarily, every time, yield particles where a single member of the "optical code" shown in figure 5 as corresponding to the "first signal generating moiety" would be present in constant amount in all particles. Indeed, the illustrative figure 5 in Nie would be an exception – because only three different types of particles are illustrated, the presence of only two different fluorophores would be sufficient to construct an adequate characterizing signal. For any fourth different particle, it would be necessary to vary the amount of the green quantum dot in order to distinguish the fourth particle unless more different colors were used.

Claims 3-6

While appellants believe that based on the principles of law set forth above, Nie does not anticipate claims to the composition (1-2 and 7), it is clear that there is no anticipation of the method claims (3-6). There is clearly no disclosure, either explicit or inherent, in Nie that the green quantum dot of figure 5 be used in a method to assess the number of particles at a given location. Nie, indeed, teaches away from this by employing for this purpose the fluorophore "F" attached to the target, not to the particle.

With respect to the outstanding rejection of claims 5-6 as obvious over the combination of Nie with Kauvar (US 2001/0044116), this depends entirely on the validity of the rejection of claim 3, which, as shown above, is in error.

Further, with respect to claim 4a, the Examiner points to figure 4a as showing that the disclosure of Nie includes the requirement that the sample be displayed on a support suitable for viewing by microscopy. The description of figure 4a does not appear to support this interpretation. The only mention of microscopy in the specification of Nie that appellants have been able to find is in paragraph 121 which is unclear as to what is being observed.

Summary of Argument:

With regard to composition claims 1, 2 and 7, Nie does not anticipate because the requirements for finding inherent anticipation are not present. Because Nie uses a "green quantum dot" illustrated in figure 5 as part of the characterizing first signal generating moiety, construction of the Nie particles will not invariably lead to the coincidental circumstance of figure 5 where a single green quantum dot is present in each different particle at the same level. There is no question that Nie fails to anticipate any method claim (claims 3-6) which require the step of using the intensity of the signal emitted from the second signal generating moiety (as assertedly illustrated in figure 5 of Nie) as a measure of the number of particles being viewed. Therefore, appellants respectfully request that the rejection of claims 1-7 be reversed.

8. Claims Appendix

An Appendix containing a copy of the claims as currently pending is attached.

9. Evidence Appendix

No evidence pursuant to §§ 1.130, 1.131, or 1.132 or entered by or relied upon by the examiner is being submitted.

10. Related Proceedings Appendix

No related proceedings are referenced in 2. above, therefore no Appendix is included.

11. Certificate of Service

Not applicable.

The Assistant Commissioner is hereby authorized to charge any additional fees under 37 C.F.R. § 1.17 that may be required by this Brief, or to credit any overpayment, to **Deposit Account No. 03-1952**.

Respectfully submitted,

Dated: January 17, 2007

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CLAIMS APPENDIX

1. (previously presented): A composition comprising a multiplicity of different labels, wherein each different label is directed to a different specific target, wherein each label consists essentially of a particulate support which support is coupled

(a) to a first characterizing signal-generating moiety which moiety comprises one or more entities that emit one or more wavelengths that compose a visible characterizing signal that characterizes said label, and

(b) to a second signal-generating moiety consisting of a single fluorophore directly attached to said particulate support which second signal-generating moiety emits a signal of the same wavelength at the same intensity from all of said different labels,

wherein the wavelength of the signal generated by said second signal-generating moiety is different from the one or more wavelengths that compose the characterizing signal, and

wherein said each label further contains at least one reagent that binds specifically to a target for said label.

2. (previously presented): The composition of claim 1, wherein said characterizing signal-generating moiety comprises at least two different signal-generating entities wherein each of the entities generates a wavelength different from that generated by the other entity(s) and wherein the resulting signals of the labels resulting from said wavelength(s) is varied among the different labels whereby each different label is thereby characterized by a different characterizing signal.

3. (previously presented): A method to determine the distribution of multiple target substances in a sample which method comprises contacting said sample with the composition of claim 1,

wherein the number of labels at a location in the sample is assessed by measuring the intensity of the signal emitted from the second signal generating moiety attached to said particulate supports,

and the nature of the target at a location in the sample is assessed by identifying the characterizing signal,

whereby the distribution of targets in the sample is determined.

4. (previously presented): The method of claim 3, wherein said sample is displayed on a support suitable for viewing by microscopy.

5. (previously presented): The method of claim 4, wherein the sample comprises an intracellular environment.

6. (previously presented): The method of claim 4, wherein the sample comprises neural circuitry.

7. (previously presented): The composition of claim 1, wherein said particulate supports have diameters of 20-200 nm.

8-9. (canceled)